Clinical Nutrition 42 (2023) 2475–2483

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Aluminum and other chemical elements in parenteral nutrition components and all-in-one admixtures

Katja A. Schönenberger [a, b, c, 1, *], Christoph Saxer [a, 1], Peter J. Neyer [a], Valentina V. Huwiler [a, b, c], Emilie Reber [c], Angelika Hammerer-Lercher [a], Zeno Stanga [c], Stefan Mühlebach [b]

[a] Institute of Laboratory Medicine, Cantonal Hospital Aarau, Tellstrasse 25, 5001 Aarau, Switzerland
[b] Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Spitalstrasse 26, 4056 Basel, Switzerland
[c] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, University of Bern, Freiburgstrasse 15, 3010 Bern, Switzerland

ARTICLE INFO

Article history:
Received 26 April 2023
Accepted 12 October 2023

Keywords:
Parenteral nutrition
Aluminum
Trace elements
Inductively coupled plasma mass spectrometry (ICP-MS)
Safety
Toxicity

SUMMARY

Background & aims: Parenteral nutrition (PN) can lead to high or even toxic exposure to aluminum (Al). We aimed to quantify concentrations of Al and other chemical elements of all-in-one (AIO) PN admixtures for adults prepared from commercial multichamber bags (Olimel® 5.7%, Omegaflex® special, SmofKabiven®, all with and without electrolytes) and vitamin and trace element additives over a 48-h period. Secondly, we determined the level of Al contamination resulting from admixing and infusion set use.

Methods: We used dynamic reaction cell and kinetic energy discrimination inductively coupled plasma mass spectrometry (ICP-MS) to quantify Al, arsenic (As), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), antimony (Sb), selenium (Se), tin (Sn), vanadium (V), and zinc (Zn) in AIO PN admixtures. We extracted samples for analysis via the bag injection ports and infusion sets over a 48-h period after admixing. We compared the measured Al concentrations of AIO PN admixtures with calculated values based on the measured concentrations of individual chamber contents and additives.

Results: Mean (standard deviation) baseline Al concentrations in AIO PN admixtures ranged from 10.5 (0.5) to 59.3 (11.4) μg/L and decreased slightly over the 48 h (estimate [standard error] -0.09 [0.02] μg/L/hour, p <0.001). Thus, certain products exceeded the widely accepted limit of 25 μg/L. There was no significant difference in Al concentrations between samples extracted via the bag injection ports or infusion sets ($p = 0.33$), nor between measured and calculated Al concentrations of AIO PN admixtures ($p = 0.91$).

Conclusion: Because certain commercially available PN admixtures for adults proved to contain excessively high levels of Al in our study, regulations and corresponding quality requirements at the authority level (e.g., Pharmacopoeia and regulatory authorities) are urgently required. Our results showed that the PN handling process (admixing and supplementing additives) or the materials of the infusion set did not lead to additional Al contamination to any extent. Moreover, calculated Al concentrations of AIO PN admixtures derived from individual chamber contents and additives are valid.

1. Introduction

Aluminum (Al) is ubiquitous in soil, air, water, food, pharmaceuticals, and cosmetic products. Although humans ingest Al through the diet, intestinal absorption is minimal [1]. However, if uptake or elimination of Al is affected, such as upon bypass of the protective gastrointestinal barrier or impaired kidney function, Al

* Corresponding author. Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Freiburgstrasse 15, 3010 Bern, Switzerland.
E-mail address: katja.schoenenberger@extern.insel.ch (K.A. Schönenberger).
[1] Co-first authors.

https://doi.org/10.1016/j.clnu.2023.10.012

Abbreviations

AIO	all-in-one
Al	aluminum
Ar	argon
As	arsenic
Cd	cadmium
Co	cobalt
Cr	chromium
Cu	copper
DRC	dynamic reaction cell
Fe	iron
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	inductively coupled plasma mass spectrometry
Mg	magnesium
Mn	manganese
Mo	molybdenum
Ni	nickel
PN	parenteral nutrition
Rh	rhodium
RPa	retarding potential analyzer
RPq	retarding potential quadrupole
Sb	antimony
SD	standard deviation
Se	selenium
Sn	tin
U.S. FDA	United States Food and Drug Administration
V	vanadium
Zn	zinc

can accumulate in tissues and exert pro-inflammatory effects as well as oxidative injuries [2,3]. Patients on parenteral nutrition (PN), especially those with prolonged administration or impaired kidney function, as well as neonates, are at significant risk for Al accumulation [3]. In adults, approximately 40% of the Al infused with PN is retained in the body [4]. Systemic Al toxicosis can lead to various pathological conditions, including pulmonary, cardiovascular, inflammatory bowel, neurologic, pancreatic, and hepatorenal diseases, anemia, sclerosis, macrophagic myofasciitis, osteomalacia, oligospermia, infertility, and breast cancer and cysts [2]. With regard to PN, metabolic bone disease, neurologic complications, and PN-associated liver disease are of particular concern [5]. Safe parenteral doses of Al range from 2 to 5 μg/kg body weight/day [6,7].

Calcium, phosphate, potassium, multivitamins, and trace elements are major sources of Al contamination in PN [8]. Raw materials can be naturally contaminated with Al, or contamination may occur during manufacturing and handling. Additionally, Al may leach from containers or contact materials [9]. Historically, substituting natural casein hydrolysate with crystalline amino acids substantially reduced Al contamination [10]. Nowadays, high Al content in PN is mostly due to contamination through calcium gluconate, inorganic phosphates, and cysteine hydrochloride [3,9]. Strategies to reduce Al contamination include substituting glass containers, which contain Al oxide, and rubber closures with plastic packaging, replacing calcium gluconate with calcium chloride, and using organic sources of phosphate [3,9]. The use of calcium chloride is controversial due to the increased risk of precipitation with inorganic phosphate salts [3,11].

Currently, there are no European regulations limiting the quantity of Al in PN and its components. However, in January 2023, the European Pharmacopoeia initiated the Aluminum in Parenteral Solutions Working Party responsible for drafting a new general chapter on Al in PN solutions to limit the risk of exposure to toxic levels of Al [12]. The United States Food and Drug Administration (U.S. FDA) mandates that the Al concentration of large-volume PN products must not exceed 25 μg/L. Additionally, specifications of small-volume parenteral drug products and pharmacy bulk packages used in the preparation of PN admixtures must disclose the maximum level of Al at expiry. Furthermore, Al concentrations must be determined with validated assay methods submitted to the U.S. FDA [7].

Infants are at the greatest risk of developing Al toxicity from PN, and because of this, there is plenty of information on Al exposure resulting from pediatric PN [8,13–28]. In adults, Al concentrations of PN admixtures used for long-term PN are not well studied. Therefore, we aimed to quantify Al in commercial PN components and all-in-one (AIO) admixtures used routinely for long-term PN in adults (Olimel® 5.7%, Omegaflex® special, SmofKabiven®, all with and without electrolytes and corresponding vitamin and trace element additives). In particular, we determined the changes in Al concentrations over a 48-h period and aimed to quantify Al contamination potentially arising from the infusion set or admixing procedures.

2. Materials & methods

2.1. Parenteral nutrition samples and analytical materials

We selected PN admixtures that are commonly used in adults in Switzerland and other European countries (Table 1) and quantified Al, arsenic (As), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), antimony (Sb), selenium (Se), tin (Sn), vanadium (V), and zinc (Zn) in the admixtures and their components. AIO admixtures were prepared from commercial three-chamber bags containing glucose solutions, amino acid solutions, and lipid emulsions, with and without electrolytes, and additives of vitamins and trace elements (specific investigated combinations of three-chamber bags and additives are shown in Fig. 1). For Al analysis, we extracted samples via the bag injection ports with a syringe as well as via the infusion set with a three-way stopcock under normal laboratory conditions at baseline and after 6, 12, 24, and 48 h at room temperature. Figure 1 shows the steps involved in preparing and sampling the AIO admixtures. In addition, we determined Al concentrations of all individual chamber contents (glucose solutions, amino acid solutions, lipid emulsions) and additives (vials) in the baseline (0 h) run. Blanks used as laboratory environment controls were treated in the same way as the test samples and were stored in the measurement cups for at least as long. To ensure quality control, we analyzed serum calibrator samples, ultrapure water blanks, and laboratory environment samples together with all analytical runs. Table 1 provides manufacturer details and lot numbers of products analyzed. Packaging and composition of PN products are detailed in Supplementary Table 1. The infusion set was made of diethylhexyl phthalate-free polyvinyl chloride and the three-way stopcock of microcrystalline polyamide.

2.2. Analytical procedure and inductively coupled plasma mass spectrometry settings

In a 2.5 mL polypropylene disposable sample cup, 200 μL of samples or standards was diluted in 1800 μL of diluent and mixed by repetitive pipetting. The diluent consisted of 500 mL of ultrapure

Table 1
Manufacturer details and lot numbers of used materials.

Product	Supplier	Lot
Parenteral nutrition mutlichamber bags		
Olimel® 5.7% 1000 mL	Baxter AG, Opfikon, Switzerland	21A15N41
Olimel® 5.7% E 1000 mL	Baxter AG, Opfikon, Switzerland	22A10N50
Omegaflex® special 1875 mL	B. Braun Medical AG, Sempach, Switzerland	220428231
Omegaflex® special without electrolytes 1875 mL	B. Braun Medical AG, Sempach, Switzerland	221458231
SmofKabiven® 986 mL	Fresenius Kabi (Schweiz) AG, Kriens, Switzerland	16RC75-1
SmofKabiven® EF 986 mL	Fresenius Kabi (Schweiz) AG, Kriens, Switzerland	16QM76-2
Vitamin additives		
Cernevit®	Baxter AG, Opfikon, Switzerland	LE22V048
Soluvit® N	Fresenius Kabi (Schweiz) AG, Kriens, Switzerland	10QL2748
Vitalipid® N Adult	Fresenius Kabi (Schweiz) AG, Kriens, Switzerland	10QE5654
Viant®	B. Braun Melsungen AG, Melsungen, Germany	39961TB21
Trace element additive		
Addaven®	Fresenius Kabi (Schweiz) AG, Kriens, Switzerland	12PMB99
Nutryelt®	Baxter AG, Opfikon, Switzerland	D0523A04
Tracutil®	B. Braun Medical AG, Sempach, Switzerland	22121050
Infusion set and devices		
Discofix® C three-way stopcock	B. Braun Melsungen AG, Melsungen, Germany	22K22D9040
Volumed® Set AirLock, 235 cm	Acromed AG, Kloten, Switzerland	22PH832
Materials for analysis		
TruQ™ms 1000 μg/mL aluminum in 2% HNO_3	PerkinElmer Inc., Waltham, Massachusetts, USA	CL13-57ALY1
ClinCal® serum calibrator, lyophilized, for trace elements	RECIPE Chemicals + Instruments GmbH, Munich, Germany	1318
ROTIPURAN® Supra 69% nitric acid	Carl Roth GmbH + Co. KG, Karlsruhe, Germany	1119101
2-Propanol, CHROMASOLV™ LC-MS, ≥99.9%	Honeywell Specialty Chemicals Seelze GmbH, Seelze, Germany	L120A
Standard 1000 μg/mL rhodium in 10% HCl	PerkinElmer, Inc., Waltham, Massachusetts, USA	23-142RHY1
BD™ Blunt Fill Needle	Becton Dickinson S.A., Fraga, Spain	1511 29
Injekt® 5 mL syringe	B. Braun Medical Inc., Bethlehem, Pennsylvania, USA	16N12C8
Injekt® 10 mL syringe	B. Braun Medical Inc., Bethlehem, Pennsylvania, USA	21F03C8
Omican® 50 syringe	B. Braun Melsungen AG, Melsungen, Germany	18L29C8

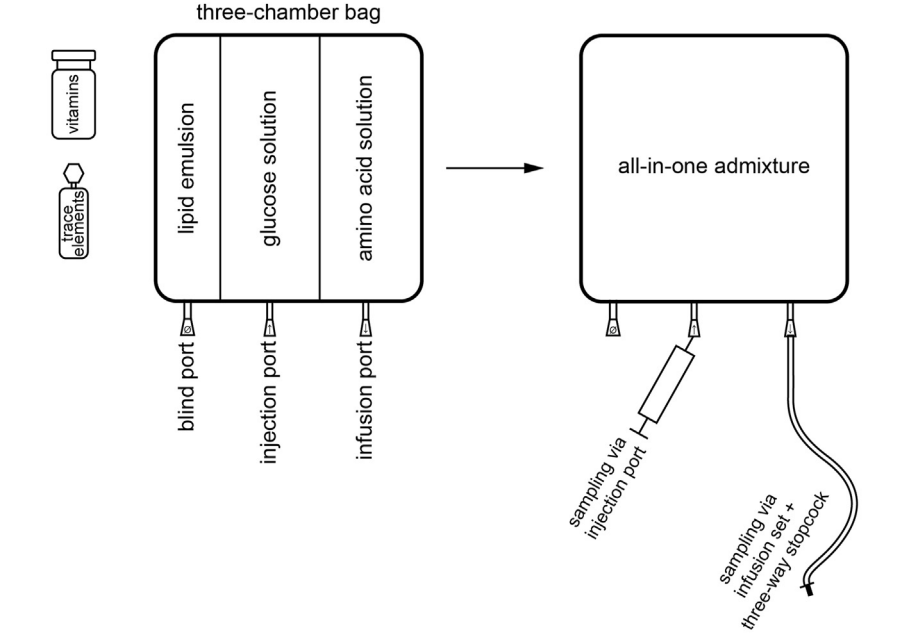

Fig. 1. Admixing of parenteral nutrition from commercial multichamber bags and vitamin and trace element additives, and sampling via the bag injection port and infusion set with a three-way stopcock.

water, 10 μL of rhodium standard, 5 mL of propan-2-ol, and 5 mL of nitric acid. Diluted samples were injected into the inductively coupled plasma mass spectrometry (ICP-MS) instrument (NexION 2000, PerkinElmer, Inc., Waltham, Massachusetts, USA) with an autosampler (Single Cell Micro DX, PerkinElmer, Inc., Waltham, Massachusetts, USA). Table 2 shows the final method specifications,

with method development details provided in the Supplementary Material.

2.2.1. Method verification

Linearity was assessed by measuring dilutions of Al reference material (see Table 1, TruQ™ms 1000 μg/mL Al in 2% HNO_3, traceable to NIST SRM #3101a) to yield the following concentrations 20′000 μg/L, 10′000 μg/L, 1′000 μg/L, 100 μg/L, 10 μg/L, 1 μg/L, 0.1 μg/L, 0.01 μg/L, and 0.001 μg/L in water and AIO PN. Each dilution was then subjected to the same analytical procedure as described above. Signals were corrected for background by subtraction of the signal from a blank sample, plotted against their theoretical concentrations and correlation coefficients were calculated as defined below. Starting from the lowest concentration, samples were sequentially excluded until linearity was reached.

Limit of quantification for Al was determined by recovery experiments with concentrations of 0.75 μg/L, 1 μg/L, 2.5 μg/L, 5 μg/L, 7.5 μg/L, 10 μg/L. All concentrations demonstrated sufficient precision to establish 1 μg/L as the lower limit of detection. The coefficient of variation for net intensities in samples spiked to 0.75 μg/L and 1.00 μg/L, measured in triplicates across three runs ($n = 9$), was 37% and 25%, respectively. Instrument method settings (gas flows, retarding potentials, dwell time) were optimized for maximum signal while specificity was accounted for by including potential multicharge interferences such as ^{54}Fe.

2.2.2. Calibration

We used a 6-point calibration series for the main analyte Al (1, 5, 25, 50, 100, 200 μg/L) and a one-point calibration for all other analytes. We calibrated the counts of the calibration standard samples linearly through zero and calculated the slope and correlation coefficient as $m = \frac{\sum xy}{\sum x^2}$ and $R = \frac{\sum xy}{\sqrt{\sum x^2} \times \sqrt{\sum y^2}}$, respectively, where x denotes the concentrations and y the intensities of the calibration standards.

Table 2
Inductively coupled plasma mass spectrometry settings.

Mass/analyte	^{103}Rh (IS) ^{27}Al ^{51}V ^{52}Cr	^{103}Rh (IS) ^{24}Mg ^{55}Mn ^{59}Co ^{57}Fe ^{60}Ni ^{63}Cu ^{66}Zn ^{75}As ^{78}Se ^{98}Mo ^{111}Cd ^{118}Sn ^{121}Sb
Mode	DRC	KED
Dwell time	50.0 ms	50.0 ms
RPa	0	0
RPq	0.5	0.25
Cell gas (NH_3) flow rate	0.6 mL/min	N/A
He flow rate	N/A	4.75 mL/min
Auxiliary gas (Ar) flow rate	1.2 mL/min	
Nebulizer gas (Ar) flow rate	0.84 mL/min	
Plasma gas (Ar) flow rate	15 L/min	
Sample introduction gas	None	
Replicates	3	
Readings/replicate	1	
Sample uptake rate	0.43 mL/min	
Cones	Nickel	
Scan mode	Peak hopping	
Sweeps/reading	15	
Dilution factor	1:10	

Abbreviations: Al, aluminum; Ar, argon; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; DRC, dynamic reaction cell; Fe, iron; IS, internal standard; KED, kinetic energy discrimination; Mg, magnesium; Mn, manganese; Mo, molybdenum; NH_3, ammonia; Ni, nickel; Rh, rhodium; RPa, retarding potential analyzer; RPq, retarding potential quadrupole; Sb, antimony; Se, selenium; Sn, tin; V, vanadium; Zn, zinc.

2.3. Calculated vs. measured aluminum concentrations of all-in-one admixtures

We compared measured Al concentrations of AIO admixtures with computations based on measured quantities of Al introduced by the individual chamber contents and vitamin and trace element additives. We calculated the concentrations as $\rho_{calculated} = \frac{\sum(\overline{\rho_{component}} \cdot V_{component})}{\sum V_{component}}$ with a standard deviation of $\sigma(\rho_{calculated}) = \frac{\sqrt{\sum(\sigma(\rho_{component}) \cdot V_{component})^2}}{\sum V_{component}}$ and total content as $m_{calculated} = \sum(\overline{\rho_{component}} \cdot V_{component})$ with a standard deviation of $\sigma(m_{calculated}) = \sqrt{\sum(\sigma(\rho_{component}) \cdot V_{component})^2}$, where components were glucose solution, amino acid solution, lipid emulsion, and additives of vitamins and trace elements.

2.4. Statistical analyses

We identified 92 outliers in 1344 triplicates using two-tailed Dixon's Q tests. These outliers (2.3% of all measurements obtained) were considered true outliers attributable to potential contamination or errors during sample workup and measurement. Therefore, we excluded these outliers from all subsequent analyses.

To assess the differences between calculated and measured Al concentrations in samples extracted via the injection port, we employed a linear mixed-effect model. The concentration determination method variable (with values of “calculated” or “measured”) was considered as fixed effect and PN admixture as random effect. To evaluate the effect of time and infusion set, we used another linear mixed-effect model. In this model, time point and sampling method (injection port vs. infusion set) were considered as fixed effects and admixture as random effect.

Statistical significance was considered at p-values <0.05. All statistical analyses were conducted using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) [29] with packages *tidyverse* version 1.3.2 [30], *outliers* version 0.15, *lme4* version 1.1.31 [31], and *lmerTest* version 3.1.3 [32].

3. Results

Figure 2 shows the measured Al concentrations in AIO PN admixtures over time and Al concentrations calculated from measurements of Al levels in the chambers and additives. Our analysis revealed no significant difference between the Al concentrations of AIO admixtures sampled via infusion sets with three-way stopcocks and those obtained via bag injection ports ($p = 0.33$), with similar results obtained when restricting the model to baseline measurements ($p = 0.18$). However, there was a significant decrease in Al concentrations of AIO admixtures over a 48-h period after admixing (estimate [standard error] -0.09 [0.02] μg/L/hour, p <0.001). Moreover, there was no significant difference between measured and calculated Al concentrations ($p = 0.91$). Table 3 presents the Al concentrations and total contents of AIO PN admixtures as calculated from measurements of individual chamber contents and additives and Supplementary Table 2 presents the body weight at which the limits of safe Al exposure are reached. Calibration curves for Al of all analytical runs are shown in Supplementary Fig. 2.

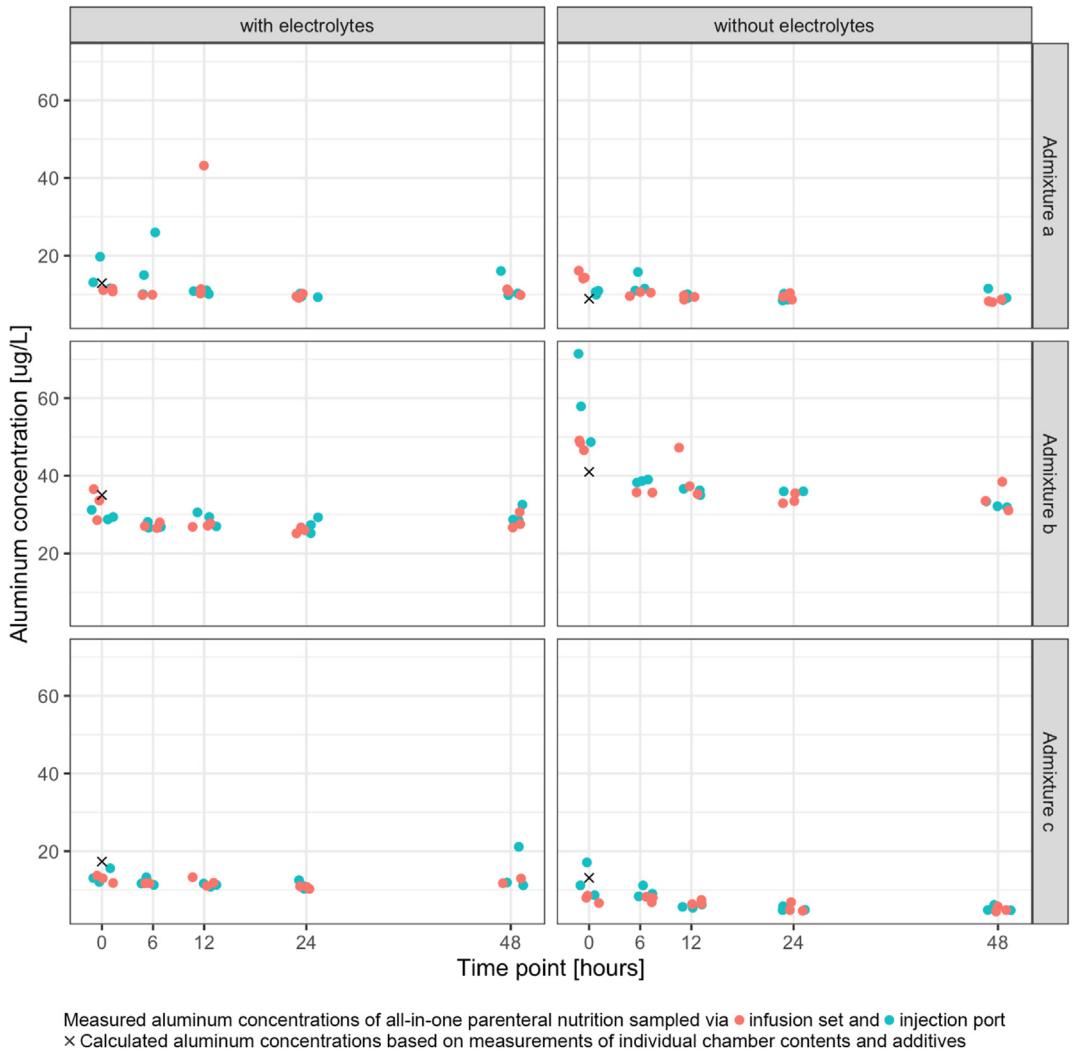

Fig. 2. Measured aluminum concentrations of parenteral nutrition admixtures (triplicates) over time and calculated aluminum concentrations based on measurements of individual chamber contents and additives (Admixture a: Olimel® 5.7% [E] 1000 mL + Cernevit® + Nutryelt®; Admixture b: Omegaflex® special [without electrolytes] 1875 mL + Tracutil®; Admixture c: SmofKabiven® [EF] 986 mL + Soluvit® + Vitalipid® + Addaven®).

Table 4 shows the concentrations of PN components for all analytes (Al, As, Cd, Co, Cr, Cu, Fe, Mg, Mn, Mo, Ni, Sb, Se, Sn, V, Zn). Concentrations of AIO admixtures over time, sampled via the bag injection port and infusion set with a three-way stopcock, are provided in Supplementary Table 1. Removal of outliers is also shown in Table 4 and Supplementary Table 1. Supplementary Table 3 shows differences between measured trace element contents and those declared by the manufacturers.

4. Discussion

The results of this study showed that Al concentrations in commercial PN products were highly variable, some of them excessively high. The Al concentrations calculated from measurements of individual chamber contents and vitamin and trace element additives were similar to the measured Al concentrations in the AIO admixtures. There was a slight decrease in Al concentrations in AIO admixtures over 48 h in the absence of additional contamination from the infusion set with a three-way stopcock. Furthermore, our study demonstrated the suitability of dynamic reaction cell (DRC)-IPC-MS for the analysis of oil-in-water PN emulsions.

None of the glucose solutions exceeded the widely accepted Al limit of 25 μg/L. However, Omegaflex® special amino acid solution without electrolytes and Omegaflex® special lipid emulsion achieved mean (standard deviation) Al concentrations of 24.5 (12.1) μg/L and 28.8 (0.7) μg/L, respectively. All admixtures with electrolytes in our study contained calcium in the form of calcium chloride (either in the glucose or amino acid solution) and phosphate as inorganic sodium salts (sodium glycerophosphate in Olimel® 5.7% and SmofKabiven®, sodium dihydrogen phosphate in Omegaflex® special). The solutions containing sodium glycerophosphate exhibited higher Al concentrations than the corresponding electrolyte-free solutions, while there was no difference between the solution containing dihydrogen phosphate and the corresponding electrolyte-free solution. However, our data do not allow to conclude whether the difference in the amino acid solutions was attributable to sodium glycerophosphate or other electrolytes, such as potassium.

Currently, there is no standard method to quantify Al in oil-in-water PN emulsions. Consequently, the validity of data obtained with variable methods may be questionable, especially if the methods used do not take the unique properties of oil-in-water emulsions into account. Our study highlights the importance of

Table 3
Aluminum concentrations and total content of all-in-one parenteral nutrition admixtures, calculated from measurement of individual chamber contents and additives.

Admixture	Most Al from	Bag size [mL]	Al [μg/L], mean (SD)	Al [μg], mean (SD)
Olimel® 5.7% E + Cernevit® + Nutryelt®	Amino acid solution	1000	12.9 (0.7)	13.2 (0.7)
		1500	12.8 (0.7)	19.5 (1.1)
		2000	12.8 (0.7)	25.9 (1.4)
Olimel® 5.7% + Cernevit® + Nutryelt®	Lipid emulsion	1000	8.9 (0.4)	9.1 (0.4)
		1500	8.8 (0.4)	13.4 (0.6)
		2000	8.8 (0.4)	17.7 (0.8)
Omegaflex® special + Viant® + Tracutil®	Tracutil®	625	75.0 (1.8)	48.4 (1.2)
		1250	45.1 (1.8)	57.3 (2.3)
		1875	34.9 (1.8)	66.1 (3.5)
Omegaflex® special EF + Viant® + Tracutil®	Tracutil®	625	80.8 (4.7)	52.1 (3.0)
		1250	51.0 (4.8)	64.7 (6.1)
		1875	40.8 (4.8)	77.4 (9.1)
SmofKabiven® + Soluvit® + Vitalipid® + Addaven®	Amino acid solution	493	18.5 (1.0)	9.7 (0.5)
		986	17.2 (1.1)	17.4 (1.1)
		1477	16.7 (1.1)	25.1 (1.6)
		1970	16.4 (1.1)	32.9 (2.2)
SmofKabiven® EF + Soluvit® + Vitalipid® + Addaven®	Amino acid solution	986	13.0 (1.0)	13.2 (1.0)
		1477	12.5 (1.0)	18.8 (1.5)

Abbreviations: Al, aluminum; SD, standard deviation.

proper method development and reporting. To the best of our knowledge, there is only one previous paper with a detailed discussion of the analytical method development and the suitability of the method to quantify Al in oil-in-water PN emulsions [33].

While it is challenging to compare our results to published data due to the variability in products, packaging, origin, and analytical methods, our findings for glucose solutions are consistent with previous studies [13,14,17,19,21,22,33–36]. However, published data on amino acid solutions and lipid emulsions vary considerably. Most studies reported Al concentrations <25 μg/L [14,19,21,22,33,34], but others reported higher concentrations [13,17,36]. Aşut et al., who also determined Al concentrations using DRC-ICP-MS, and Menédez et al. reported extremely high Al concentrations in large-volume PN products (up to 2350 μg/L in glucose solutions, 1640 μg/L in amino acid solutions, and 2200 μg/L in lipid emulsions) [15,35]. Of note, Aşut et al. found the highest Al concentrations among lipid emulsions in SMOFlipid® 20%, which is the same lipid emulsion we analyzed as part of the SmofKabiven® EF bag in our study. However, neither our results nor those reported by Lima-Rogel et al. [19] confirmed the high Al concentrations reported by Aşut et al. [15]. Alongside manufacturing and methodological differences that might have contributed to the elevated Al concentrations reported by Aşut et al., the notably high Al concentration in SMOFlipid® 20% observed in their study could be attributable to differing storage containers. Specifically, SMOFlipid® 20% analyzed by Aşut et al. was stored in a glass container (personal communication), whereas in our study, it was stored in a polymeric Biofine® bag.

The Tracutil® trace element additive contained excessively high Al amounts, causing final AIO admixtures to exceed the 25 μg/L limit by approximately 1.5–3 times, depending on the bag size. The three trace element additives analyzed were comparable in terms of the trace elements composition but Tracutil® was the only one with glass packaging investigated. However, all investigated vitamin additives were also stored in glass containers and did not contain particularly high Al concentrations. Aşut et al. reported even higher Al concentrations in Tracutil® [15].

Generally, published data on other multitrace element and multivitamin additives indicate more marked Al contamination than that found in our study [13–15,17,22,35]. Nevertheless, our study supports the criticality of micronutrient addition to the AIO PN admixtures in terms of Al exposure. The variability in Al concentrations stresses the importance of defining quality standards for these medicinal products for parenteral use, as initiated by the European Pharmacopoeia [12].

The comparable Al concentrations in analyzed admixture samples and calculated estimations confirmed the absence of significant Al contamination introduced during aseptic admixing in a laboratory environment. It is important to note that this refers to the mixing of the compartments of multichamber bags in a closed system and adding vitamins and trace elements via the injection port. Prior studies estimating Al concentrations from measurements of components used for pharmaceutical PN compounding found higher Al concentrations if measured rather than estimated. De Oliveira et al. stipulated that 35% of Al contents is contributed by the bag admixing procedure [15,17]. However, calculations based on Al levels of components as reported by manufacturers tend to overestimate total Al contents of admixtures [18,20–22,37]. To enable pharmacists to calculate the total Al content of PN admixtures, manufacturers should state the exact Al concentrations instead of indicating the maximum Al level accepted or making a general statement that the Al concentration of the product is below 25 μg/L.

De Oliveira et al. found that 9% of the total Al content was contributed by the administration set (of unknown material), with most of the Al being released upon the initial flow through the tube [17]. However, we observed no increase in Al concentrations when sampling the liquid through a universally used infusion set (diethylhexyl phthalate-free polyvinyl chloride) with three-way stopcock (microcrystalline polyamide) instead of extracting samples via a syringe inserted into the injection port of the bag. Therefore, estimations of Al exposure from PN admixtures based on calculations from the individual components appear to be valid for these widely used multichamber bags supplemented with vitamin and trace element additives.

Al concentrations decreased slightly over 48 h after admixing, covering the maximally accepted period between the preparation of the AIO admixture and administration to the patient. However, the small decrease of approximately 1 μg Al/L 12 h after admixing is not relevant from a safety perspective.

Assuming a PN dose of one AIO admixture bag per day, adult patients remain within the safe Al exposure of 4–5 μg/kg body weight/day [7], despite the high Al concentrations in some of the tested PN products and AIO admixtures. However, when considering Al infusions of 2 μg/kg body weight/day as safe, as suggested by the American Society for Clinical Nutrition and American Society

Table 4
Mean (SD) concentrations of elements quantified in parenteral nutrition components.

Parenteral nutrition component	Al [μg/L]	As [μg/L]	Cd [μg/L]	Co [μg/L]	Cr [μg/L]	Cu [μg/L]	Fe [mg/L]	Mg [mg/L]	Mn [μg/L]	Mo [μg/L]	Ni [μg/L]	Sb [μg/L]	Se [μg/L]	Sn [μg/L]	V [μg/L]	Zn [mg/L]
Addaven®	17.8 (0.6)	0.2 (0.0)[a]	0.8 (0.1)	0.8 (0.0)	1008.7 (16.1)	42130.6 (1111.3)	112 (4)	<0.1	5377.4 (4.7)[a]	1971.9 (58.3)	5.7 (0.3)	0.1 (0.0)	9252.7 (230.5)	0.2 (0.1)	0.1 (0.0)	666 (17)
Cernevit®	11.2 (0.6)	0.1 (0.1)	<0.1[a]	27.5 (0.3)	2.7 (0.1)	1.0 (0.1)	<1	<0.1	0.4 (0.0)	1.2 (0.0)	0.8 (0.0)	1.1 (0.0)	<2	<0.1	<0.1[a]	<0.1
Nutryelt®	40.7 (19.5)	<0.1	2.6 (0.0)[a]	10.1 (0.2)	965.7 (19.3)	32945.4 (158.8)	103 (1)	<0.1	5263.8 (52.5)	2107.7 (8.3)	9.2 (0.3)	<0.1	7124.9 (107.1)	0.3 (0.1)	4.8 (0.1)	1276 (4)
Olimel® 5.7% amino acid solution	16.5 (1.4)	0.2 (0.0)	<0.1	0.9 (0.0)	3.2 (0.0)	2.7 (0.3)	<1	261.6 (1.1)	3.7 (0.1)	0.7 (0.0)	2.4 (0.1)	4.0 (0.1)	2.2 (0.1)	0.2 (0.1)	0.4 (0.0)	<0.1
Olimel® 5.7% amino acid solution without electrolytes	6.7 (0.4)	<0.1	<0.1	1.2 (0.0)	1.4 (0.1)	1.9 (0.1)	<1	<0.1	0.7 (0.1)	0.2 (0.0)	1.7 (0.0)	<0.1	<2	<0.1	<0.1	<0.1
Olimel® 5.7% glucose solution	5.5 (0.7)	0.6 (0.1)	<0.1	<0.1	0.4 (0.2)	9.2 (10.5)	<1	0.2 (0.0)	1.4 (1.2)	2.6 (2.8)	1.3 (0.0)[a]	<0.1	2.9 (4.6)	<0.1	<0.1	0 (0)
Olimel® 5.7% glucose solution without electrolytes	5.1 (0.0)[a]	0.7 (0.1)	<0.1	<0.1	0.1 (0.0)	0.5 (0.0)	<1	<0.1	0.3 (0.0)	0.2 (0.0)	1.2 (0.1)	<0.1	2.5 (1.4)	<0.1	<0.1	<0.1
Olimel® 5.7% lipid solution	19.2 (1.8)	0.3 (0.1)	<0.1	0.2 (0.0)	0.4 (0.1)	7.3 (0.2)	<1	<0.1	0.2 (0.0)	0.2 (0.1)	0.7 (0.1)	<0.1	<2	<0.1	<0.1	<0.1
Omegaflex® special amino acid solution	11.5 (2.5)	0.1 (0.0)	0.2 (0.1)	0.1 (0.0)	10.8 (0.0)[a]	1.7 (0.1)	<1	269.7 (0.7)	17.1 (0.0)[a]	1.6 (0.1)	5.9 (0.3)	0.1 (0.0)	4.5 (0.7)	0.3 (0.0)	0.4 (0.0)	<0.1
Omegaflex® special amino acid solution without electrolytes	24.5 (12.1)	<0.1	<0.1	<0.1	5.2 (0.2)	1.2 (0.0)	<1	0.2 (0.0)	10.6 (0.0)[a]	0.9 (0.0)	3.3 (0.2)	<0.1	<2	0.5 (0.1)	<0.1	<0.1
Omegaflex® special glucose solution	9.6 (3.9)	1.4 (0.1)	<0.1	<0.1	1.3 (0.1)	7.0 (7.0)	<1	<0.1[a]	0.8 (0.0)[a]	7.1 (6.5)	2.3 (0.1)	0.4 (0.0)	2.8 (2.8)	<0.1	0.1 (0.0)	7 (0)[a]
Omegaflex® special glucose solution without electrolytes	11.5 (0.7)	0.2 (0.0)	<0.1	<0.1	0.5 (0.0)	3.3 (1.2)	<1	<0.1	2.2 (0.6)	0.7 (0.2)	0.9 (0.1)	<0.1	2.1 (0.8)	0.1 (0.0)	<0.1	<0.1
Omegaflex® special lipid solution	28.8 (0.7)	0.4 (0.2)	<0.1	0.5 (0.0)	0.5 (0.0)	4.4 (0.0)	<1	0.2 (0.0)	1.5 (0.1)	0.5 (0.1)	1.0 (0.1)	<0.1	7.9 (0.4)	0.4 (0.2)	1.2 (0.0)	<0.1
SmofKabiven® amino acid solution	21.7 (2.1)	1.2 (1.7)	0.1 (0.1)[a]	<0.1	4.4 (0.1)	1.2 (0.2)	<1	246.3 (5.3)	5.1 (0.3)	1.4 (0.3)	2.0 (0.2)	3.0 (0.5)	<2	0.1 (0.0)[a]	0.3 (0.0)	6 (0)
SmofKabiven® amino acid solution without electrolytes	13.3 (2.0)	<0.1	<0.1	<0.1	1.7 (0.1)	1.2 (0.1)	<1	<0.1	1.4 (0.1)	0.4 (0.1)	1.6 (0.0)[a]	<0.1	<2	<0.1	<0.1	<0.1
SmofKabiven® glucose solution	9.7 (0.6)	1.7 (0.2)	<0.1	<0.1	0.2 (0.0)	0.8 (0.2)	<1	<0.1	0.3 (0.1)	0.1 (0.1)	1.2 (0.1)	<0.1	<2[a]	<0.1	<0.1	<0.1
SmofKabiven® lipid solution	9.1 (0.0)[a]	1.0 (0.2)	<0.1	0.1 (0.0)	0.2 (0.0)	6.3 (0.0)	<1	0.2 (0.0)	0.4 (0.2)	0.4 (0.0)	0.6 (0.1)	0.1 (0.1)	<2	<0.1	<0.1	<0.1
Soluvit®	12.6 (0.5)	0.5 (0.1)	<0.1	21.8 (0.5)	0.9 (0.0)	0.8 (0.0)	<1	<0.1[a]	0.2 (0.1)	0.9 (0.0)[a]	0.6 (0.1)	<0.1	<2	<0.1	<0.1	<0.1
Tracutil®[b]	3940.5 (11.9)	0.3 (0.0)	0.6 (0.1)	0.9 (0.1)	1090.4 (1.4)	87588.3 (353.4)	208 (1)	<0.1	55169.7 (271.7)	1004.6 (10.4)	6.8 (0.2)	<0.1[a]	2314.5 (57.9)	140.7 (1.0)	0.3 (0.0)	434 (3)
Viant®	10.8 (6.2)	0.6 (0.1)	<0.1	19.9 (0.4)	4.4 (0.1)	0.8 (0.1)	<1[a]	<0.1	0.9 (0.5)	0.7 (0.0)	7.9 (0.1)	<0.1[a]	<2	<0.1	0.2 (0.0)[a]	<0.1
Vitalipid®	166.7 (1.7)	0.4 (0.1)	0.1 (0.1)	<0.1[a]	0.9 (0.0)	9.3 (0.1)	<1[a]	0.1 (0.0)	0.4 (0.0)	0.4 (0.0)	2.0 (0.2)	1.0 (0.0)	<2	<0.1	<0.1	<0.1

Abbreviations: Al, aluminum; As, arsenic; Cd, cadmium; Co, cobalt; Cr, chromium; Cu, copper; Fe, iron; Mg, magnesium; Mn, manganese; Mo, molybdenum; Ni, nickel; Sb, antimony; SD, standard deviation; Se, selenium; Sn, tin; V, vanadium; Zn, zinc.

[a] One of three samples excluded as outlier.

[b] Repeated measurement in a later analytical run (48-h time point) confirmed Al concentrations with a different Tracutil® vial from the same batch, diluent, and calibration curve. Mean (standard deviation) Al concentration in the repeated measurement was 4204 (63) μg/L.

for Parenteral and Enteral Nutrition [6], patients with a low body weight (<39 kg for Omegaflex® special EF + Viant® + Tracutil®) may exceed the limits of safe Al exposure with some of the tested AIO admixtures.

Considering the safety risks associated with other contaminants of PN, such as small cationic heavy metals, none of the PN admixtures analyzed in this study exhibited concentrations exceeding the maximum daily exposures permitted as defined by the ICH guideline Q3D (R1) on elemental impurities [38] for the secondary analytes As, Cd, Co, Cr, Ni, Sb, Sn, and V. The trace element contents of Addaven® and Nutryelt® declared by the manufacturers were in line with our results, while we measured about 90% less trace elements in Tracutil® than declared by the manufacturer for all investigated trace elements (Cr, Cu, Fe, Mn, Mo, Se, Zn). This difference in measured and declared trace element content of Tracutil® was confirmed by a repeated measurement in a later analytical run with a different vial, diluent, and calibration curve.

To the best of our knowledge, this is the first study determining Al in AIO PN admixtures prepared from widely used multichamber bags for adults. This constitutes a major advance over previous investigations of PN regimens for adults that examined only individual components but not the admixture [34–36]. Harigaya et al. [33] evaluated an admixture that lacked lipids and trace elements, while Speerhans et al. [37] did not report the composition of PN admixtures they analyzed.

4.1. Strengths and limitations

The main strength of our study was the use of a DRC-ICP-MS method which we specifically developed to quantify Al in oil-in-water PN admixtures with a very low limit of detection. Our method featured a 6-point calibration series, and we conducted multiple analytical runs with a new calibration curve for each run. In addition, we measured triplicates of each sample to enable outlier identification and removal from analyses. Moreover, we accounted for environmental influences by analyzing various control samples (i.e. water blank, laboratory environment controls, and serum quality control samples). However, interpretation of our results is limited by the lack of data on lot-to-lot variability of the products tested. Moreover, the tested AIO admixtures may not be fully representative on an international level as we exclusively used combinations that are commonly available in Switzerland.

5. Conclusion

Certain large-volume PN products and admixtures, including those intended for long-term use in adults, exceed the widely accepted limit of 25 μg/L. Therefore, regulations of Al concentrations in PN products are urgently needed on both the European and global level. Moreover, analytical specifications to quantify Al contents of different matrices (aqueous solutions vs. oil-in-water emulsions) such as those presented in this study must be developed. Our results showed that the PN handling process (admixing multichamber bags and supplementing additives) or the materials of the infusion set did not lead to additional Al contamination to any extent. Therefore, labeling of PN components with their actual Al content enables accurate calculations of overall Al exposure from PN.

Funding statement

This work was supported by a third-party grant of the Division of Clinical Pharmacy and Epidemiology, University of Basel [grant number FO119900]. Open access funding was provided by the University of Basel and swissuniversities.

Author contribution

Katja A. Schönenberger: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing - original draft **Christoph Saxer:** Conceptualization, Investigation, Methodology, Project administration, Writing - review & editing **Peter J. Neyer:** Conceptualization, Methodology, Writing - review & editing **Valentina V. Huwiler:** Investigation, Methodology, Writing - review & editing **Emilie Reber:** Conceptualization, Writing - review & editing **Angelika Hammerer-Lercher:** Resources, Supervision, Writing - review & editing **Zeno Stanga:** Supervision, Writing - review & editing **Stefan Mühlebach:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

Conflict of interest

There are no conflicts of interest.

Acknowledgments

The authors thank the laboratory staff at the Institute of Laboratory Medicine, Cantonal Hospital Aarau, for their invaluable support and cooperation in conducting the analyses, the Department of Clinical Research of the University of Basel for statistical consulting, and Dr. Silvia Rogers for academic editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.10.012.

References

[1] Safety of aluminium from dietary intake - scientific opinion of the panel on food additives, flavourings, processing aids and food contact materials (AFC). EFSA J 2008;6. https://doi.org/10.2903/j.efsa.2008.754.
[2] Igbokwe IO, Igwenagu E, Igbokwe NA. Aluminium toxicosis: a review of toxic actions and effects. Interdiscipl Toxicol 2019;12:45–70. https://doi.org/10.2478/intox-2019-0007.
[3] Hernandez-Sanchez A, Tejada-Gonzalez P, Arteta-Jimenez M. Aluminium in parenteral nutrition: a systematic review. Eur J Clin Nutr 2013;67:230–8. https://doi.org/10.1038/ejcn.2012.219.
[4] Klein GL, Ott SM, Alfrey AC, Sherrard DJ, Hazlet TK, Miller NL, et al. Aluminum as a factor in the bone disease of long-term parenteral nutrition. Trans Assoc Am Phys 1982;95:155–64.
[5] Gura KM. Aluminum contamination in parenteral products. Curr Opin Clin Nutr Metab Care 2014;17:551–7. https://doi.org/10.1097/MCO.0000000000000091.
[6] ASCN/A.S.P.E.N. Working Group on Standards for Aluminum Content of Parenteral Nutrition Solutions. Parenteral drug products containing aluminum as an ingredient or a contaminant: response to Food and Drug Administration notice of intent and request for information. JPEN - J Parenter Enter Nutr 1991;15:194–8. https://doi.org/10.1177/0148607191015002194.
[7] Code of Federal Regulations § 201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition. Washington, D.C: Food and Drug Administration, Department of Health and Human Services; 2003. at http://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-201/subpart-G/section-201.323. [Accessed 31 May 2023].
[8] Hall AR, Arnold CJ, Miller GG, Zello GA. Infant parenteral nutrition remains a significant source for aluminum toxicity. JPEN - J Parenter Enter Nutr 2017;41:1228–33. https://doi.org/10.1177/0148607116638056.
[9] Bohrer D. Aluminum in subjects receiving parenteral nutrition. In: Rajendram R, Preedy VR, Patel VB, editors. Diet and nutrition in critical care. New York: Springer; 2015. p. 2049–64.
[10] Vargas JH, Klein GL, Ament ME, Ott SM, Sherrard DJ, Horst RL, et al. Metabolic bone disease of total parenteral nutrition: course after changing from casein to amino acids in parenteral solutions with reduced aluminum content. Am J Clin Nutr 1988;48:1070–8. https://doi.org/10.1093/ajcn/48.4.1070.
[11] Gura KM. Aluminum contamination in products used in parenteral nutrition: has anything changed? Nutrition 2010;26:585–94. https://doi.org/10.1016/j.nut.2009.10.015.
[12] European Directorate for the Quality of Medicines & HealthCare. Call for experts – aluminium in parenteral nutrition solutions. Strasbourg, France:

Council of Europe; 2023. https://www.edqm.eu/en/-/call-for-experts-aluminium-in-parenteral-nutrition-solutions. [Accessed 13 February 2023].
[13] Advenier E, Landry C, Colomb V, Cognon C, Pradeau D, Florent M, et al. Aluminum contamination of parenteral nutrition and aluminum loading in children on long-term parenteral nutrition. J Pediatr Gastroenterol Nutr 2003;36:448–53. https://doi.org/10.1097/00005176-200304000-00005.
[14] Alvarez L, Rebollido M, Fernandez-Lorenzo JR, Cocho JA, Fraga JM. Electrothermal atomic absorption spectrometry determination of aluminium in parenteral nutrition and its components. J Trace Elem Med Biol 2007;21(Suppl 1):29–30. https://doi.org/10.1016/j.jtemb.2007.09.009.
[15] Aşut E, Köksal N, Dorum BA, Özkan H. Aluminum exposure in premature babies related to total parenteral nutrition and treatments. Turk J Pediatr 2018;60:385–91. https://doi.org/10.24953/turkjped.2018.04.005.
[16] Courtney-Martin G, Kosar C, Campbell A, Avitzur Y, Wales PW, Steinberg K, et al. Plasma aluminum concentrations in pediatric patients receiving long-term parenteral nutrition. JPEN - J Parenter Enter Nutr 2015;39:578–85. https://doi.org/10.1177/0148607114531046.
[17] de Oliveira SR, Bohrer D, Garcia SC, do Nascimento PC, Noremberg S. Aluminum content in intravenous solutions for administration to neonates: role of product preparation and administration methods. JPEN - J Parenter Enter Nutr 2010;34:322–8. https://doi.org/10.1177/0148607110362531.
[18] Huston RK, Heisel CF, Vermillion BR, Christensen JM, Minc L. Aluminum content of neonatal parenteral nutrition solutions: options for reducing aluminum exposure. Nutr Clin Pract 2017;32:266–70. https://doi.org/10.1177/0884533616668789.
[19] Lima-Rogel V, Romano-Moreno S, de Jesús López-López E, de Jesús Escalante-Padrón F, Hurtado-Torres GF. Aluminum contamination in parenteral nutrition admixtures for low-birth-weight preterm infants in Mexico. JPEN - J Parenter Enter Nutr 2016;40:1014–20. https://doi.org/10.1177/0148607114550001.
[20] Migaki EA, Melhart BJ, Dewar CJ, Huston RK. Calcium chloride and sodium phosphate in neonatal parenteral nutrition containing TrophAmine: precipitation studies and aluminum content. JPEN - J Parenter Enter Nutr 2012;36:470–5. https://doi.org/10.1177/0148607111420154.
[21] Poole RL, Pieroni KP, Gaskari S, Dixon TK, Park K, Kerner Jr JA. Aluminum in pediatric parenteral nutrition products: measured versus labeled content. J Pediatr Pharmacol Therapeut 2011;16:92–7. https://doi.org/10.5863/1551-6776-16.2.92.
[22] Poole RL, Schiff L, Hintz SR, Wong A, Mackenzie N, Kerner Jr JA. Aluminum content of parenteral nutrition in neonates: measured versus calculated levels. J Pediatr Gastroenterol Nutr 2010;50:208–11. https://doi.org/10.1097/MPG.0b013e3181aed70b.
[23] Mouser JF, Wu AH, Herson VC. Aluminum contamination of neonatal parenteral nutrient solutions and additives. Am J Health Syst Pharm 1998;55:1071–2. https://doi.org/10.1093/ajhp/55.10.1071.
[24] Popińska K, Kierkuś J, Lyszkowska M, Socha J, Pietraszek E, Kmiotek W, et al. Aluminum contamination of parenteral nutrition additives, amino acid solutions, and lipid emulsions. Nutrition 1999;15:683–6. https://doi.org/10.1016/s0899-9007(99)00124-0.
[25] Koo WW, Kaplan LA, Bendon R, Succop P, Tsang RC, Horn J, et al. Response to aluminum in parenteral nutrition during infancy. J Pediatr 1986;109:877–83. https://doi.org/10.1016/s0022-3476(86)80718-1.
[26] Koo WW, Kaplan LA, Horn J, Tsang RC, Steichen JJ. Aluminum in parenteral nutrition solution—sources and possible alternatives. JPEN - J Parenter Enter Nutr 1986;10:591–5. https://doi.org/10.1177/0148607186010006591.
[27] Larchet M, Chaumont P, Galliot M, Bourdon R, Goulet O, Ricour C. Aluminium loading in children receiving long-term parenteral nutrition. Clin Nutr 1990;9:79–83. https://doi.org/10.1016/0261-5614(90)90057-y.
[28] Hayes P, Martin TP, Pybus J, Hunt J, Broadbent RS. Reduction of bioavailability of aluminium in neonatal parenteral nutrition solutions by prior complexation in the dosage form. J Parenter Sci Technol 1992;46:169–75.
[29] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2022. URL, https://www.R-project.org.
[30] Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, et al. Welcome to the tidyverse. J Open Source Softw 2019;4. https://doi.org/10.21105/joss.01686.
[31] Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Software 2015;67. https://doi.org/10.18637/jss.v067.i01.
[32] Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. J Stat Software 2017;82. https://doi.org/10.18637/jss.v082.i13.
[33] Harigaya K, Kuwahara Y, Nishi H. Determination of aluminum in large volume parenteral drug products used in total parenteral nutrition therapy by ICP-MS with a dynamic reaction cell. Chem Pharm Bull (Tokyo) 2008;56:475–9. https://doi.org/10.1248/cpb.56.475.
[34] Brown RO, Morgan LM, Bhattacharya SK, Johnson PL, Minard G, Dickerson RN. Potential aluminum exposure from parenteral nutrition in patients with acute kidney injury. Ann Pharmacother 2008;42:1410–5. https://doi.org/10.1345/aph.1L061.
[35] Menendez AM, Farias SS, Servant R, Morisio Y, Misischia Y, Simon S, et al. [Aluminum content in individual components, used to prepare adult total parenteral nutrition mixtures in Argentine, and in comparison with international regulation]. Nutr Hosp 2014;29:1380–7. https://doi.org/10.3305/nh.2014.29.6.7320.
[36] Öztürk E, Yıldırım S, Akyol A. Determination of aluminum concentrations of parenteral nutrition solutions by HPLC. Eur J Clin Nutr 2021;75:567–9. https://doi.org/10.1038/s41430-020-00741-0.
[37] Speerhas RA, Seidner DL. Measured versus estimated aluminum content of parenteral nutrient solutions. Am J Health Syst Pharm 2007;64:740–6. https://doi.org/10.2146/ajhp060468.
[38] European Medicines Agency Committee for Human Medicinal Products. International Council on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) guideline Q3D (R1) on elemental impurities. 2019.